Wnt signaling inhibition by monensin results in a period of Hippo pathway activation during intestinal adaptation in zebrafish.

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Public Summary:
Intestinal adaptation (IA) is a critical response to increase epithelial surface area after intestinal loss. Short bowel syndrome (SBS) may follow massive intestinal resection in human patients, particularly without adequate IA. We previously validated a model in zebrafish (ZF) that recapitulates key SBS pathophysiological features. Previous RNA sequencing in this model identified upregulation of genes in the Wnt and Hippo pathways. We therefore sought to identify the timeline of increasing cell proliferation and considered the signaling that might underpin the epithelial remodeling of IA in SBS. SBS was created in a ZF model as previously reported and compared with sham fish with and without exposure to monensin, an ionophore known to inhibit canonical Wnt signaling. Rescue of the monensin effects was attempted with a glycogen synthase kinase 3 inhibitor that activates wnt signaling, CHIR-99021. A timeline was constructed to identify peak cellular proliferation, and the Wnt and Hippo pathways were evaluated. Peak stem cell proliferation and morphological changes of adaptation were identified at 7 days. Wnt inhibition diminished IA at 2 wk and resulted in activation of genes of the Wnt/beta-catenin and Yes-associated protein (YAP)/Hippo pathway. Increased cytoplasmic YAP was observed in monensin-treated SBS fish. Genes of the WASP-interacting protein (WIP) pathway were elevated during Wnt blockade. In conclusion, cellular proliferation and morphological changes accompany SBS even in attempted Wnt blockade. Wnt/beta-catenin, YAP/Hippo pathway, and WIP pathway genes increase during early Wnt blockade. Further understanding of the effects of Wnt and YAP pathway signaling in proliferating stem cells might enrich our knowledge of targets to assist IA. NEW & NOTEWORTHY Intestinal adaptation is a critical response to increase epithelial surface area after large intestinal losses. Inhibition of Wnt/beta-catenin signaling impairs intestinal adaptation in a zebrafish model of short bowel syndrome. There is a subsequent upregulation in genes of the Yes-associated protein/Hippo and WIP pathway. These may be targets for future human therapies, as patients are salvaged by the compensation of increased intestinal epithelial surface area through successful intestinal adaptation.

Scientific Abstract:
Intestinal adaptation (IA) is a critical response to increase epithelial surface area after intestinal loss. Short bowel syndrome (SBS) may follow massive intestinal resection in human patients, particularly without adequate IA. We previously validated a model in zebrafish (ZF) that recapitulates key SBS pathophysiological features. Previous RNA sequencing in this model identified upregulation of genes in the Wnt and Hippo pathways. We therefore sought to identify the timeline of increasing cell proliferation and considered the signaling that might underpin the epithelial remodeling of IA in SBS. SBS was created in a ZF model as previously reported and compared with sham fish with and without exposure to monensin, an ionophore known to inhibit canonical Wnt signaling. Rescue of the monensin effects was attempted with a glycogen synthase kinase 3 inhibitor that activates wnt signaling, CHIR-99021. A timeline was constructed to identify peak cellular proliferation, and the Wnt and Hippo pathways were evaluated. Peak stem cell proliferation and morphological changes of adaptation were identified at 7 days. Wnt inhibition diminished IA at 2 wk and resulted in activation of genes of the Wnt/beta-catenin and Yes-associated protein (YAP)/Hippo pathway. Increased cytoplasmic YAP was observed in monensin-treated SBS fish. Genes of the WASP-interacting protein (WIP) pathway were elevated during Wnt blockade. In conclusion, cellular proliferation and morphological changes accompany SBS even in attempted Wnt blockade. Wnt/beta-catenin, YAP/Hippo pathway, and WIP pathway genes increase during early Wnt blockade. Further understanding of the effects of Wnt and YAP pathway signaling in proliferating stem cells might enrich our knowledge of targets to assist IA. NEW & NOTEWORTHY Intestinal adaptation is a critical response to increase epithelial surface area after large intestinal losses. Inhibition of Wnt/beta-catenin signaling impairs intestinal adaptation in a zebrafish model of short bowel syndrome. There is a subsequent upregulation in genes of the Yes-associated protein/Hippo and WIP pathway. These may be targets for future human therapies, as patients are salvaged by the compensation of increased intestinal epithelial surface area

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